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<b>(54) Title:</b> A PHARMACEUTICAL COMPOSITION COMPRISING CYCLOSPORIN IN A LIPID CARRIER		
<b>(57) Abstract</b>  A pharmaceutical composition comprising a cyclosporin as an active substance in a lipid carrier, which carrier comprises membrane lipids in combination with monoglycerides and optionally non-polar lipids, which composition is characterized in being liquid at room temperature and containing 0.5-25 % cyclosporin, 10-45 % membrane lipids, 10-55 % monoglycerides and 0-45 % non-polar lipids. A composition of the invention is bioequivalent to a commercial drug containing in addition to cyclosporin and additives also toxic emulsifiers and ethanol.		

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## A PHARMACEUTICAL COMPOSITION COMPRISING CYCLOSPORIN IN A LIPID CARRIER

The present invention refers to a new formulation of a cyclosporin for oral administration giving an improved uptake.

**Background of the invention**

Cyclosporins are a group of biologically active metabolites produced by different species of fungi imperfecti. The major components, cyclosporins A and C are non-polar cyclic oligopeptides with immunosuppressive, antifungal and antiphlogistic activity. Today a number of minor metabolites have been identified, all being highly hydrophobic oligopeptides. The major use of cyclosporins is to prevent organ rejection after transplantation.

Cyclosporin A, cyclosporine or ciclosporin, is a cyclic oligopeptide consisting of 11 amino acids. The exact mechanism of action of cyclosporine is not known, but it is believed that the effect is due to a specific and reversible inhibition of immunocompetent lymphocytes. Cyclosporine is commercially available under the registered trade marks Sandimmun Neoral®, Neoral® or Sandimmune®, as soft gelatin capsules, an oral solution or as a concentrate for injection. Said formulations all contain more than 10 % ethanol. The absorption of cyclosporine, administered as Sandimmun Neoral®, Neoral® or Sandimmune®, from the gastro-intestinal tract is, however, incomplete and variable and it is recommended that transplant patients taking the soft gelatin capsules or the oral solution over a period of time are monitored at repeated intervals for cyclosporine blood levels to avoid toxicity due to high levels, and possible organ rejection due to low absorption, respectively.

**Prior art**

US 4,388,307 refers to a pharmaceutical composition comprising a pharmacologically effective amount of a cyclosporin and a carrier, wherein the carrier comprises a) a transesterification product of a natural vegetable oil, b) a vegetable oil, and c) ethanol. Said composition could be

formulated as a drink solution or as capsules for oral administration. The use of ethanol is, however, not desirable and may also cause difficulties when the composition is presented in soft gelatin encapsulated form.

5 In GB 2 228 198 B it is proposed to use a carrier medium for a cyclosporin which comprises b) a fatty acid triglyceride, c) a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester, and d) a  
10 tenside having a hydrophilic-lipophilic balance (HLB) of at least 10. By this it would be possible to obtain oil-based compositions of a cyclosporin which do not require the presence of solvents or solubilizers such as ethanol. The  
15 tensides used in the examples are different ethoxylated reaction products, such as Cremophor RH 40, Tween, and Pluronic. The compositions obtained are said to provide a reduced variability in cyclosporine blood levels. It is, however, a well known fact that ethoxylated surfactants might be the cause of allergenic reactions, partly because of  
20 oxidation when exposed to air, and thus should be avoided in medical treatment.

Lipophilic carrier systems have also been described, WO 95/20945 for instance discloses a lipophilic carrier preparation having a continuous lipid phase comprising a polar lipid material in combination with a non-polar lipid. The polar  
25 lipid material should be a galactolipid material consisting of at least 50 % digalactosyldiacylglycerols and a remainder of other polar lipids. In Example 2 of said publication a preparation of a lipophilic carrier containing 5 % cyclosporin A, in combination with a galactolipid material and  
30 evening primrose oil is disclosed. Said galactolipid material had been obtained by an industrially applicable process for preparing glycosylglycerides from plants, preferably cereals, by means of extraction and chromatographic separations.

WO 92/05771 describes a lipid particle forming matrix of  
35 at least two lipid components; one is non-polar and another is amphiphatic and polar. This particle forming matrix, which can contain bioactive materials, spontaneously forms discrete lipid particles when interacting with aqueous systems. The amphiphatic and polar lipid components are said to be bilayer

forming and are chosen from phospholipids such as phosphatidylcholine; the non-polar lipids are mono-, di- or triglycerides.

5     **Description of the invention**

It has now surprisingly been found that a formulation of a cyclosporin in a lipid carrier consisting of a fractionated vegetable oil in combination with monoglycerides and non-polar lipids will give an uptake of the cyclosporin in blood which is bioequivalent to the uptake of cyclosporin from a commercial drug containing in addition to cyclosporin and additives also toxic emulsifiers and ethanol.

According to FDA a standard bioequivalence can be defined as a range of 80% to 120% of the product averages for a broad range of drugs (USP 24 NF 19, 2058).

The present invention refers to a new pharmaceutical composition comprising a cyclosporin as an active substance in a lipid carrier, which carrier comprises membrane lipids in combination with monoglycerides and optionally non-polar lipids, which is characterized in being liquid at room temperature and containing the following in % by weight of the total composition

	cyclosporin	0.5-25 %
	membrane lipids	10-45 %
25	monoglycerides	10-55 %
	non-polar lipids	0-45 %

The invention especially refers to a pharmaceutical composition wherein the lipid carrier contains 15-20 % membrane lipids, 25-50 % monoglycerides and 5-30 % non-polar lipids.

According to another aspect of the invention the lipid carrier of the pharmaceutical composition contains 15-45 % membrane lipids and 25-50 % monoglycerides.

Membrane lipids, preferably natural membrane lipids for the sake of biocompatibility and safety, which are all polar lipids, can broadly be defined as belonging to any of the categories phospholipids, glycolipids and sphingolipids.

Phospholipids, mainly soy or egg lecithin derived from soybeans and egg respectively, or made by synthetic routes

contain different phospholipid classes, which can be zwitter-ionic, such as phosphatidylcholine and phosphatidylethanolamine classes, or negatively charged, such as phosphatidylinositol or phosphatidylglycerol classes.

5 Glycolipids from plants contain glycolipids which have carbohydrate units, mainly of galactose, linked to glycerol. Glycosylglycerides are a type of glycolipids which are well-known constituents of plant cell membranes. The most  
10 important classes of these contain one to four sugars linked glycosidically to diacylglycerol. The two most abundant classes contain one and two galactose units, respectively, and are commonly known as mono- and digalactosyldiacylglycerol, MGDG and DGDG representing up to 40 % of the dry weight of the thylakoid membranes. Galactolipids, primarily  
15 DGDG and DGDG-rich materials, have been investigated and found to be a surface active material of interest in industrial application such as food, cosmetics, and pharmaceutical applications.

Synthetic diglycosyldiacylglycerols based on galactose or  
20 any other monosaccharide unit, such as glucose, and natural glycosylglycerides, isolated from any source, based on other carbohydrate units than galactose, such as glucose, can be used in accordance with the invention.

An intrinsic beneficial feature of the galactolipids is  
25 the galactose units comprising the polar head group in each lipid molecule, which may sterically stabilise the emulsion droplets in an emulsion. The galactose groups may also interact strongly with water and other polar substances, such as a water-soluble drug or an excipient, added to the  
30 emulsion. In investigating the interaction of the glycosylglycerides with non-polar or slightly polar lipids, such as mono-, di- and triglycerides, fatty alcohols and acids, sterols and sterol esters, optionally combined with other polar lipids such as phospholipids and sphingolipids, without  
35 water, or with only small amounts of water, it has been found a behaviour which makes such preparations suitable as lipophilic carriers.

According to a preferred aspect of the invention the membrane lipids of the pharmaceutical composition contain

phospholipids and galactolipids. Especially the membrane lipids of the pharmaceutical composition contain DGDG in admixture with phosphatidylcholine.

Galactolipids can be prepared from almost any kind of plant material, for instance according to WO 95/20945 by extraction of the lipids with ethanol and a subsequent purification on a chromatographic column. Preferred plant materials are seeds and kernels from grains and cereals, for instance wheat, rye, oats, and barley. Oat groats as well as wheat gluten have a high lipid concentration and are therefore of advantage to use in the preparation process. A galactolipid material consisting of 50-70 % digalactosyldiacylglycerols and 30-50 % other polar lipids is manufactured by Scotia LipidTeknik AB, Stockholm, as CPL®-Galactolipid (registered trade mark owned by Scotia Holdings PLC). The other polar lipids being part of said galactolipid material are a mixture of different glyco- and phospholipids, such as MGDG and phosphatidylcholines.

WO 97/11141 describes a method for producing a fractionated vegetable oil which is characterised in containing 10-90 % by weight of polar lipids, preferably 20-75 %, and a remainder of non-polar lipids. Said fractionated vegetable oil contains galactolipids and can also be used for providing the membrane lipids of the invention. The fractionated vegetable oil preferably contains more than 5 % by weight, preferably more than 20 %, glycolipids and preferably more than 3 % by weight, preferably more than 15 %, DGDG. According to a preferred embodiment of the invention the fractionated oil is oat oil consisting of 40-60 % polar lipids and a remainder of non-polar lipids. The composition depends on the starting material and process used for the manufacture of the galactolipids. A fractionated oat oil of this composition consisting of a wide range of polar and amphiphilic lipids in a continuous triglyceride phase is manufactured by Scotia LipidTeknik AB, Stockholm, as Galactolec™, and is also referred to as galactolecithin.

Sphingolipids can be obtained from milk raw materials by extraction and purification, for instance by chromatography, and contain for example sphingomyelin in combination with

phosphatidylcholine, mono- and dihexocylceramides and triglycerides. Sphingolipids are a family of lipids based on sphingosine in contrast to the ones previously described which are based on glycerol. Examples of sphingolipids are sphingomyelin, mono- and dihexosylceramides, and gangliosides.

According to a preferred aspect of the invention the membrane lipids should contain DGDG in an amount of 0.1 - 90 % by weight based on the membrane lipids, preferably 10 - 70 %.

Monoglycerides or monoacylglycerols are slightly polar in nature and possess certain surface active properties. They can be obtained by fractionation of vegetable or animal oils. Preferred monoglycerides of the invention are of a medium chain length, that is having a fatty acid chain of 8-12 carbon atoms, especially 8-10 carbon atoms, and can be obtained from coconut and palm kernel oil.

Monoglycerides in combination with the membrane lipids facilitate the formation of lipid particles of the pharmaceutical composition in the gastro-intestinal tract.

Non-polar lipids are for example natural or synthetic di- or triacylglycerols, such as, or derived from, vegetable oils, animal oils, synthetic glycerides, fatty acids, fatty alcohols, sterols, such as cholesterol, and their esters with fatty acids. The chain length and the degree of saturation of the glycerides should be chosen to give a liquid composition.

Preferably the non-polar lipids of the pharmaceutical composition comprises mainly triacylglycerols.

The invention especially refers to a pharmaceutical composition of cyclosporine in a lipid carrier comprising a mixture of a fractionated vegetable oil and monoglycerides.

A preferred composition of the invention comprises, in % by weight of the total composition, 8-12 % cyclosporin, 40-50 % galactolecithin, and 40-50 % MCM, that is C8-C10 monoacylglycerols.

A pharmaceutical composition of the invention preferably comprises cyclosporin A, that is cyclosporine.

Generally a pharmaceutical composition of the invention can be prepared by mixing, optionally after melting in an



open water bath at a temperature range of 40-70°C, non-polar lipids, such as triglycerides, and the monoglycerides with a cyclosporin and the membrane lipids in a vial. The mixture is then dispersed with a high shear mixer at approximately 1000 rpm and at a temperature range of 40-70°C for 2-4 min. The mixture can optionally contain increasing contents of water or aqueous solution which can lead to the formation of reverse vesicles, reverse micelles or a water-in-oil emulsion. If the lipid mixture is hard to melt or if the content of cyclosporin is high it might be necessary first to dissolve the mixture in ethanol, which is subsequently evaporated.

The pharmaceutical composition is mainly intended for oral administration, but can also be used for enteral, rectal, vaginal, topical, ocular, nasal or aural administration to animals, especially mammals, including humans.

In addition to the essential ingredients the pharmaceutical composition of the invention can also contain conventional additives and excipients, such as antiseptic agents, preservatives, thickening agents, pigments, flavouring and the like, in combinations as needed.

Oral unit dosage forms, such as soft or hard gelatin capsules, can comprise from 5 to 200 mg, preferably from 20 to 100 mg of active substance, that is a cyclosporin, for administration 1-5 times a day.

#### **Examples of cyclosporine formulations**

The membrane lipid material used in the following examples was a galactolipid material, Galactolec™ (from Scotia LipidTeknik AB, Sweden), manufactured from oats in accordance with the process described in WO 97/11141 and referred to as galactolecithin. Said galactolecithin is composed by about 60 % non-polar lipids and about 40 % polar lipids. DGDG constitutes about 20 % by weight of the total mixture.

The cyclosporin used in the formulations below was cyclosporine, that is cyclosporin A (USP XXIII, Medial AG, Switzerland).

Example 1.

	Ingredient	% by weight
5	Galactolecithin	67.5
	Akoline MCM	20
	Cyclosporine	12.5

33.751 g of galactolecithin was weighed into a 100 ml beaker together with 10.007 g of Akoline MCM, that is a mixture of C8-C10 mono- (60%), di- (32%) and tri- (8%) acylglycerols (from Karlshamns AB, Sweden), and 6.245 g of cyclosporine. The mixture was homogenized by means of a magnetic stirrer for approximately 36 hours. A yellow/brown, cloudy, highly viscous liquid was obtained.

15

Example 2.

	Ingredient	% by weight
	Galactolecithin	30
	MCM	60
20	Cyclosporine	10

3.00 g galactolecithin was weighed into a 250 ml round-bottomed flask together with 18.01 g MCM, that is C8-C10 monoacylglycerols (having a purity of 99 %, fractionated from Akoline MCM by Scotia LipidTeknik AB), and 9.00 g of cyclosporine. The mixture was homogenized by means of a spatula and heated to 60°C under magnetic stirring until the active substance and the lipids had been dissolved. The final product obtained was a yellow brown transparent solution.

25

Example 3.

	Ingredient	% by weight
30	Galactolecithin	87.5
	Cyclosporine	12.5

Using the same procedure as in Example 2 and mixing the galactolecithin with 3.01 g cyclosporine, a final product was obtained having the same appearance as the final product of Example 2.

35

Example 4.

	Ingredient	% by weight
	Galactolecithin	45
5	Akoline MCM	45
	Cyclosporine	10

By using the same procedure as in Example 2 and mixing 13.50 g galactolecithin, 13.00 g Akoline MCM, and 3.01 g cyclosporine a final product was obtained having the same appearance as the final product of Example 2.

Example 5.

	Ingredient	% by weight
	Galactolecithin	45
15	MCM	45
	Cyclosporine	10

By using the same procedure as in Example 2 and mixing 13.50 g galactolecithin, 13.51 g MCM and 3.00 g cyclosporine a final product was obtained having the same appearance as the final product of Example 2.

Example 6.

	Ingredient	% by weight
	Galactolecithin	30
25	Akoline MCM	60
	Cyclosporine	10

By using the same procedure as in Example 2 and mixing 9.01 g galactolecithin, 18.01 g Akoline MCM and 3.00 g cyclosporine a final product was obtained having the same appearance as the final product of Example 2.

Comparative Example 1.

A formulation in accordance with WO 95/20945 was prepared by mixing the following ingredients

	Ingredient	% by weight
35	GL	20.0
	EPO	67.5
	AP	0.02
	Cyclosporine	12.50

GL refers to a galactolipid material, CPL®-Galactolipid (from Scotia LipidTeknik AB, Sweden), containing about 60 % DGDG, manufactured from oats in accordance with the process described in WO 95/20945. EPO stands for evening primrose oil  
5 (from Scotia Pharmaceuticals Ltd, UK), and AP stands for ascorbyl palmitate.

Additional formulations of cyclosporine were prepared having the composition as stated in the following Table 1,  
10 wherein

CS = cyclosporine  
G-lec = galactolecithin, Galactolec™  
GL = galactolipid material, CPL®-Galactolipid  
h-GL = hydrogenated galactolipid material  
15 SL = sphingolipid material  
h-PE = hydrogenated phosphatidylethanolamine  
MCT = medium chain triacylglycerol, from Karlshamns AB  
A MCM = Akoline MCM  
Palm = palm oil, from Karlshamns AB  
20 Soy = soybean oil  
CH = cholesterol, from Apoteksbolaget AB  
PC = phosphatidylcholine, from Lucas Meyer  
SL, h-GL and h-PE were obtained from Scotia LipidTeknik AB.  
Soy bean oil is a long-chain C16-C20 triglyceride, CPL®-  
25 Soybean oil from Scotia LipidTeknik AB.

The formulations according to Examples 7-9, 11, 13 and 14 were prepared using ethanol as described in the following procedure referring to the formulation of Example 13.

13.123 g of hydrogenated galactolipid was weighed up in a  
30 250 ml round-bottomed flask together with 2.627 g Akoline MCM, 10.513 g of CPL®-Soybean oil and 3.753 g of cyclosporine. 40 ml of 95 % ethanol was then added to the flask. The flask was put in a Rotavapor (Büchi, Switzerland) and was heated to 70°C and stirred for ten minutes until the  
35 substance and the lipid had been dissolved. Then the product was evaporated to complete dryness at a temperature of 70°C for a drying time of 80 minutes. 30.02 g of a final product was obtained.

Table 1. Cyclosporine formulations

Example No.	Ingredients %	appearance
7	12.5 % CS 43.8 % GL 8.8 % A MCM 35 % Palm	yellow, solid
8	12.5 % CS 43.8 % GL 8.8 % A MCM 35 % MCT	brown, liquid
9	30 % CS 35 % GL 7 % A MCM 28 % MCT	brown, liquid, cloudy
10	12.5 % CS 20% SL 10 % CH 30 % G-lec 27.5 % MCT	white, yellow cream
11	12.5 % CS 21.9 % SL 43.4 % G-lec 4.4 % A MCM 17.5 % Soy	yellow, solid, suspension
12	12.5 % CS 15 % PC 20 % A MCM 52.5 % MCT	yellow, clear liquid
13	12.5 % CS 43.8 h-GL 8.8 % A MCM 35 % Soy	white, solid
14	12.5 % CS 17.5 % h-PE 48.1 % G-lec 4.4 % A MCM 17.5 % Soy	brown, solid

**Biological test of cyclosporine formulations**

Absorption tests were performed to study the effect of oral administration of different formulations of cyclosporine

in a soft gelatin capsule in comparison to the commercial drug Sandimmun Neoral® (known in most countries as Neoral®), soft gelatin capsules containing 100 mg cyclosporin A, that is cyclosporine, in ethanol as a reference composition. The composition of Sandimmun Neoral® per capsule was in addition to 100 mg cyclosporine and 100 mg ethanol, DL- $\alpha$ -tokoferol, propylene glykol, corn oil, Polyoxyl 40 Hydrogenated Castor Oil (Cremophor RH 40), and colours.

The biological absorption studies were performed in healthy male volunteers. The exclusion criteria were known intolerance to cyclosporine, deviations of clinical relevance, blood donor in the last two months, medical treatment which might interfere with the tests, smoking. The studies were of an open, cross-over design where the majority of the subjects received two treatments after one reference treatment, that is each subject was its own control. Each formulation was tested on three subjects and there were also three subjects who only received the reference composition on all occasions in order to estimate the intraindividual variation. The amount of cyclosporine was the same in all treatments. The intraindividual variation of Sandimmun Neoral® based on 3 subjects at 3 different observations was 15 %. The interindividual variation, that is the variation in uptake of Sandimmun Neoral® after administration once only to 18 different subjects was 21 %.

During the first visit informed consent and medical history were obtained from the subjects. Haematology and clinical chemistry analyses were performed. At the following three visits the subjects arrived at 7.00 in the morning, fasting since 22.00 the previous evening. The drug was taken about 7.30 together with approximately 150 ml of tap water. For obtaining blood samples an intravenous indwelling catheter in an arm vein was used. A series of blood samples for analysis of cyclosporine were obtained according to the following schedule: Predose, 30, 60 and 90 minutes after dose, then 2, 2.5, 3, 3.5, 4, 5.5, 7.5, 10, 12, 24, 30 and 48 hours after dose. Lunch was served 4 hours after the drug intake and the subjects were allowed to drink tea, coffee and water. The total amount of blood drawn during the study was

less than 400 ml.

The concentration of the active substance cyclosporine in blood was assessed by a specific method at the Clinical Chemistry laboratory, University Hospital, Lund. Cyclosporine analysis was performed on a Hitachi 917, using an EMIT- (Enzyme Multiple Immunoassay Technique) kit from DADE Behring.

The formulations of Example 1 (in duplicate) and Example 3 according to the invention were tested, as well as the formulation of Comparative Example 1 and the formulations of Examples 7-14.

The following relative absorption values relative to the Sandimmun Neoral®, reflecting the area under curve, AUC, were obtained.

Table 2. Relative absorption of cyclosporine, AUC<sub>t</sub>, t = 12h

Example No.	Subject 1	Subject 2	Subject 3
Comp. Ex. 1	0.45	0.53	0.67
Ex. 1	0.66	0.92	1.09
Ex. 1	0.43	0.86	0.89
Ex. 10	0.01	0.02	0.02
Ex. 12	0.12	0.12	0.98*
Ex. 3	0.50	0.62	0.70
Ex. 7	0.25	0.28	0.45
Ex. 8	0.36	0.38	0.64
Ex. 9	0.09	0.15	0.21
Ex. 11	0.42	0.47	0.61
Ex. 13	0.32	0.34	0.42
Ex. 14	0.46	0.49	0.52

\* Subject 3 is considered an outlier

These results show that by varying the amounts of the lipid components of the carrier pharmaceutical compositions can be obtained having different, and sometimes a

surprisingly improved uptake.

The absorption test described was repeated in order to test the compositions according to Examples 2, and 4-6 as to uptake in comparison to Sandimmun Neoral®.

5 The average value of the uptake and the standard deviation of all tested compositions, reflecting also the inter-individual variation, are given in the following Table 3.

Table 3.

Averaged relative absorption of cyclosporine,  $AUC_t$ ,  $t = 12h$

10	Example No.	Uptake* %	Uptake % standard deviation
	1	81	24
	2	50	4
	3	61	10
15	4	98	27
	5	80	5
	6	69	22
	7	33	11
	8	46	16
20	9	15	6
	10	2	-
	11	50	10
	12	12	-
	13	36	5
25	14	49	3
	Comp. Ex.1	55	11

\* Average of 3 subjects in comparison to the uptake of Sandimmun Neoral®



## Conclusion

From the above tests can be concluded that the compositions of Examples 1, 4 and 5 can be considered to be bioequivalent to the commercial drug Sandimmun Neoral®, as  
5 having a relative uptake  $\geq 80$  %. It should be noted that said compositions according to the invention do not contain any harmful additives, but only non-toxic lipids.

It seems to be of importance that the final pharmaceutical composition is liquid at room temperature; cf  
10 Examples 7, 11, 13 and 14 which are all solid at room temperature. It can be concluded that the physical state of the pharmaceutical composition matters for the uptake of the active substance in the gastro-intestinal tract.

Too high contents of cyclosporin will also affect the uptake; this is obvious from Example 9.  
15

Monoglycerides are of importance for the uptake. From Examples 3, 8, 10 and also 9, having a monoglyceride content below 10 %, can be concluded that too low a content of monoglycerides will negatively affect the uptake. This is  
20 also true if the content of monoglycerides is too high; Example 2 has a monoglyceride content of 60 %, bringing about a high viscosity and a poor uptake.

From the results can also be concluded that the content of non-polar lipids must not be too high. Example 12 and  
25 Comparative Example 1 both contain too much triglycerides to give an adequate uptake.

The improved variation of the composition of Example 5 compared to the composition of Example 4 is believed to derive from the defined monoglyceride fraction used in  
30 Example 5, alternatively on the low content of diglycerides. The number of tests is, however, not sufficient for a statistical confirmation thereof.

## CLAIMS

1. A pharmaceutical composition comprising a cyclosporin as an active substance in a lipid carrier, which carrier comprises membrane lipids in combination with monoglycerides and optionally non-polar lipids, which is characterized in being liquid at room temperature and containing the following in % by weight of the total composition
- |                  |          |
|------------------|----------|
| cyclosporin      | 0.5-25 % |
| membrane lipids  | 10-45 %  |
| monoglycerides   | 10-55 %  |
| non-polar lipids | 0-45 % . |
2. A pharmaceutical composition according to claim 1, wherein the lipid carrier contains 15-20 % membrane lipids, 25-50 % monoglycerides and 5-30 % non-polar lipids in % by weight of the total composition.
3. A pharmaceutical composition according to claim 1, wherein the lipid carrier contains 15-45 % membrane lipids and 25-50 % monoglycerides.
4. A pharmaceutical composition according to any of claims 1-3, wherein the membrane lipids contain DGDG in an amount of 0.1 - 90 % by weight, preferably 10 - 70 %.
5. A pharmaceutical composition according to any of claims 1-4, wherein the membrane lipids contain phospholipids and galactolipids.
6. A pharmaceutical composition according to any of claims 1-5, wherein the membrane lipids contain DGDG in admixture with phosphatidylcholine.
7. A pharmaceutical composition according to any of claims 1, 2, 4 and 5, wherein the non-polar lipids mainly comprises

triacylglycerols.

8. A pharmaceutical composition according to any of claims  
1, 2, 4-7, wherein the lipid carrier comprises a mixture of a  
5 fractionated vegetable oil and monoglycerides.

9. A pharmaceutical composition according to claim 8,  
comprising in % by weight of the total composition

	cyclosporin	8-12 %
10	galactolecithin	40-50 %
	MCM	40-50 %

10. A pharmaceutical composition according to any of  
claims 1-9, wherein the cyclosporin is cyclosporin A.

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/02259

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/13, A61K 9/107

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2222770 A (SANDOZ LTD), 21 March 1990 (21.03.90), page 23, line 8 - line 12, claim 23	1-3,5,7-8,10
A	--	4,6,9
X	US 5529785 A (HANS DIETL), 25 June 1996 (25.06.96)	1-3,5,7-8,10
A	--	4,6,9
X	WO 9613273 A1 (SANDOZ LTD ET AL), 9 May 1996 (09.05.96), page 8, line 6 - page 9, line 24; page 12, line 6 - line 7	1-3,5,7-8,10
A	--	4,6,9

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"I" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 March 2000

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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	WO 9900002 A2 (CHONG KUN DANG CORP.), 7 January 1999 (07.01.99), claim 18	1-3,5,7-8,10
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